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EXAMINER	
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ART UNIT	PAPER NUMBER
1655	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/646,892	Dolores et al.
Examiner	**Art Unit**
Arun Chakrabarti	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- *If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.*
- *If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.*
- *Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).*
- *Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).*

Status

1) ☒ *Responsive to communication(s) filed on* Nov 15, 2000 .

2a) ☐ *This action is* **FINAL.** 2b) ☒ *This action is non-final.*

3) ☐ *Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.*

Disposition of Claims

4) ☒ *Claim(s)* 1-26 *is/are pending in the application.*

4a) *Of the above, claim(s)* _____ *is/are withdrawn from consideration.*

5) ☐ *Claim(s)* _____ *is/are allowed.*

6) ☒ *Claim(s)* 1-26 *is/are rejected.*

7) ☐ *Claim(s)* _____ *is/are objected to.*

8) ☐ *Claims* _____ *are subject to restriction and/or election requirement.*

Application Papers

9) ☐ *The specification is objected to by the Examiner.*

10) ☐ *The drawing(s) filed on* _____ *is/are objected to by the Examiner.*

11) ☐ *The proposed drawing correction filed on* _____ *is: a)* ☐ *approved b)* ☐ *disapproved.*

12) ☐ *The oath or declaration is objected to by the Examiner.*

Priority under 35 U.S.C. § 119

13) ☒ *Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).*

a) ☒ *All* b) ☐ *Some** c) ☐ *None of:*

1. ☒ *Certified copies of the priority documents have been received.*
2. ☒ *Certified copies of the priority documents have been received in Application No.* 09/646,892 .
3. ☐ *Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).*

**See the attached detailed Office action for a list of the certified copies not received.*

14) ☐ *Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).*

Attachment(s)

15) ☒ *Notice of References Cited (PTO-892)*

16) ☐ *Notice of Draftsperson's Patent Drawing Review (PTO-948)*

17) ☐ *Information Disclosure Statement(s) (PTO-1449) Paper No(s).* _____

18) ☐ *Interview Summary (PTO-413) Paper No(s).* _____

19) ☐ *Notice of Informal Patent Application (PTO-152)*

20) ☐ *Other:*

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 19-20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19 and 20 are rejected over the recitation of the phrase, "accessory molecules". It is not clear if the claimed molecules are essential part of the invention or just adding to the convenience or effectiveness of the claimed cells transformed with the vector. It is also not clear what kind of molecules are classified as accessory molecules and how it is adding to the convenience or effectiveness of the claimed cells transformed with the vector. The metes and bounds of the claims are vague and indefinite.

Claims 19 is also rejected over the recitation of the phrase, "able to express"because it is unclear whether the limitations following the phrase are part of the claimed invention.

Regarding claim 20, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 22 is rejected over the use of improper Markush language. The proper language "from the group consisting of" should be used.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

4. Claims 1-3, 7-10, 13-18 and 23 are rejected under 35 U.S. C 102 (e) as being anticipated by Ward et al. (U.S. Patent 6,165,745) (December 26, 2000).

Ward et al teach a basic vector for preparing a TCR expression vector, which possesses an expression control sequence operatively linked to a polycistronic expression unit (Abstract and Figure 8) comprising:

(a) at least a part of the nucleotide sequence encoding a C region of the TCRalpha chain, with at least one restriction cleavage site being located in the 5' region of the nucleotide sequence (Figures 3 and 8 and Example 1), and

(b) at least a part of the nucleotide sequence encoding a C region of the TCRbeta chain, with at least one restriction cleavage site being located in the 5' region of the nucleotide sequence (Figures 3 and 8 and Example 1).

Ward et al teach a vector characterized in that it can be propagated in eukaryotic mammalian cells (Column 10, lines 38-40).

Ward et al teach a vector characterized in that it is a plasmid (Example 1).

Ward et al teach a vector characterized in that the expression unit allows an expression of the TCRalpha chain which is limited as compared with expression of the TCRbeta chain (Column 21, lines 19-24).

Ward et al teach a vector characterized in that at least one of the restriction cleavage sites located in the 5' region of the nucleotide sequences encoding the C regions of the TCRalpha and TCRbeta chains is unique (Figures 1, 3, 8 and Example 1).

Ward et al teach a vector characterized in that the restriction cleavage sites do not result in any amino acid substitution in the C regions (Figure 1 and Example 1).

Ward et al teach a TCR expression vector, which possesses an expression control sequence operatively linked to a polycistronic expression unit (Abstract and Figure 8) comprising:

(a) a nucleotide sequence encoding a complete TCRalpha chain (Figures 1A and 1B and Example 1), and

(b) a nucleotide sequence encoding a complete TCRbeta chain (Figures 1A and 1B and Example 1), with the nucleotide sequences encoding the V regions and C regions of the TCR chains being linked to each other by way of restriction cleavage sites in the 5' region of the C regions (Figures 1A and 1B and Example 1).

Ward et al teach a TCR expression vector characterized in that the nucleotide sequences encoding the TCR chains possess at least one base substitution, as compared with the natural TCR sequence, in the region of the restriction cleavage sites, with the base substitutions being selected within the context of the degeneracy of the genetic code (Example 1, Column 29, lines 40-46 and Figure 1).

Ward et al teach a process for preparing a TCR expression vector (Abstract), comprising the steps of :

(a) preparing a basic vector for preparing a TCR expression vector, which possesses an expression control sequence operatively linked to a polycistronic expression unit (Abstract and Figure 8) comprising:

(b) at least a part of the nucleotide sequence encoding a C region of the TCRalpha chain, with at least one restriction cleavage site being located in the 5' region of the nucleotide sequence (Figures 3 and 8 and Example 1), and

© at least a part of the nucleotide sequence encoding a C region of the TCRbeta chain, with at least one restriction cleavage site being located in the 5' region of the nucleotide sequence (Figures 3 and 8 and Example 1), and

(d) inserting nucleotide sequences which contain the regions encoding a desired V region of a TCRalpha and TCRbeta chain into the restriction cleavage sites which are located in the 5' regions of the nucleotide sequences encoding the C regions (Example 1, Column 29, lines 40-46 and Figure 1).

Ward et al teach a cell, characterized in that it is transformed with a basic TCR expression vector (Examples 2-3).

Ward et al teach a process for expressing a T cell receptor, characterized in that a suitable host cell is transformed with an expression vector and the cell is cultured under conditions which lead to the T cell receptor being expressed (Example 3, Column 32, lines 37-58).

5. Claims 1-3, 8, 11, 13 and 16-23 are rejected under 35 U.S. C 102 (e) as being anticipated by Eshar et al. (U.S. Patent 5,906,936) (May 25, 1999).

Eshar et al teach a basic vector for preparing a TCR expression vector, which possesses an expression control sequence operatively linked to a polycistronic expression unit (Abstract and Figure 8) comprising:

(a) at least a part of the nucleotide sequence encoding a C region of the TCRalpha chain, with at least one restriction cleavage site being located in the 5' region of the nucleotide sequence (Figure 8), and

(b) at least a part of the nucleotide sequence encoding a C region of the TCRbeta chain, with at least one restriction cleavage site being located in the 5' region of the nucleotide sequence (Figure 8).

Eshar et al teach a vector characterized in that it is a plasmid (Column 6, lines 30-36).

Eshar et al teach a vector characterized in that it can be propagated in human T cell lines (Figure 4).

Eshar et al teach a cell characterized in that it is able to express one or more accessory molecule such as IL-2 (Figure 1).

Eshar et al teach a vector characterized in that a BamHI cleavage site is located in the 5' region of the DNA sequence encoding the C region of the TCRalpha chain (Column 6, lines 8-16).

Eshar et al teach a TCR expression vector, which possesses an expression control sequence operatively linked to a polycistronic expression unit (Abstract and Figure 8) comprising:

(a) a nucleotide sequence encoding a complete TCRalpha chain (Figure 8), and

(b) a nucleotide sequence encoding a complete TCRbeta chain (Figures 1A and 1B and Example 1), with the nucleotide sequences encoding the V regions and C regions of the TCR chains being linked to each other by way of restriction cleavage sites in the 5' region of the C regions (Figure 8).

Eshar et al teach a cell, characterized in that it is transformed with a basic TCR expression vector (Figures 4 and 5).

Eshar et al teach a process for expressing a T cell receptor, characterized in that a suitable host cell is transformed with an expression vector and the cell is cultured under conditions which lead to the T cell receptor being expressed (Figure 6 and column 8, lines 51-66).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-4, 8, 11, 13 and 16-23 are rejected under 35 U.S. C 103 (a) over Eshar et al. (U.S. Patent 5,906,936) (May 25, 1999) in view of Bitler et al. (U.S. Patent 6,140,484) (October 31, 2000).

Eshar et al teach 1-3, 8, 11, 13 and 16-23 as described above.

Eshar et al do not teach a vector which can be replicated episomally.

Bitler et al teach a vector which can be replicated episomally.(Column 40, lines 12-18).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the vector which can be replicated episomally

of Bitler et al. in the TCR expression vector of Eshar et al, since Bitler et al. state, "The vector also replicates episomally, which may be advantageous in use with the present invention, since episomal replication typically yields higher expression levels for the first six months following transfection as compared with integrated DNA. The vector is also useful in both transient and stable expression studies (Example 4, Column 40, lines 12-18)". By employing scientific reasoning and in order to improve the expression levels for the first six months following transfection , one ordinary artisan would have combined episomally replicable vector with TCR expression vector. An ordinary practitioner would have been motivated by the express statements of Bitler et al to substitute and combine the vector which can be replicated episomally of Bitler et al. in the TCR expression vector of Eshar et al. in order to achieve the express advantages, as noted by Bitler et al., of an episomally replicable vector that typically yields higher expression levels for the first six months following transfection as compared with integrated DNA and which is also useful in both transient and stable expression studies.

8. Claims 1-3, 8, 11-13 and 16-23 are rejected under 35 U.S. C 103 (a) over Eshar et al. (U.S. Patent 5,906,936) (May 25, 1999) in view of Waldron (U.S. Patent 6,048,730) (April 11, 2000).

Eshar et al teach 1-3, 8, 11, 13 and 16-23 as described above.

Eshar et al do not teach SalI cleavage site.

Waldron teach the usefulness of SalI cleavage site in a vector (Figure 1 and Column 4, lines 34-36).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the SalI cleavage site in a vector of Waldron in the method of Eshar et al., since Waldron states, "The unique SalI cloning site provides a convenient cleavage site for insertion of a gene of interest (Column 4, lines 34-36)." By employing scientific reasoning, one ordinary artisan would have combined the SalI cleavage site in the vector of Eshar et al. to improve and customize a vector preparation. An ordinary practitioner would have been motivated to substitute and combine the SalI cleavage site in a vector of Waldron in the method of Eshar et al. in order to achieve the express advantages, as noted by Waldron, of a cleavage site which provides a convenient cleavage site for insertion of a gene of interest.

9. Claims 1-3, 5, 8, 11, 13 and 16-23 are rejected under 35 U.S. C 103 (a) over Eshar et al. (U.S. Patent 5,906,936) (May 25, 1999) in view of Wagner et al. (U.S. Patent 5,846,949) (December 8, 1998).

Eshar et al teach 1-3, 8, 11, 13 and 16-23 as described above.

Eshar et al do not teach the sequence which allows the polycistronic transcription product to be translated in a capping-independent manner.

Wagner et al teach the sequence which allows the polycistronic transcription product to be translated in a capping-independent manner (Figure 2 and Column 3, lines 28-33).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the sequence which allows the polycistronic

transcription product to be translated in a capping-independent manner of Wagner et al. in the method of Eshar et al., since Wagner et al. state, "DNA molecule further comprises a capping independent sequence that allows the translation of uncapped RNA in mammalian cells (Claims 5 and 11)." By employing scientific reasoning, one ordinary artisan would have combined the DNA molecule comprising a capping independent sequence in the vector of Eshar et al. to improve the expression of uncapped TCR mRNA in mammalian cells. An ordinary practitioner would have been motivated to substitute and combine the sequence which allows the polycistronic transcription product to be translated in a capping-independent manner of Wagner et al. in the method of Eshar et al. in order to achieve the express advantages, as noted by Wagner et al., of a DNA molecule that comprises a capping independent sequence that allows the translation of uncapped RNA in mammalian cells.

10. Claims 1-3, 6, 8, 11, 13 and 16-23 are rejected under 35 U.S. C 103 (a) over Eshar et al. (U.S. Patent 5,906,936) (May 25, 1999) in view of Beach et al. (U.S. Patent 6,025,192) (February 15, 2000).

Eshar et al teach 1-3, 8, 11, 13 and 16-23 as described above.

Eshar et al do not teach a vector characterized in that the expression unit contains an IRES sequence.

Beach et al. teach a vector characterized in that the expression unit contains an IRES sequence (Figures 1 and 2 and Column 15, lines 20-37).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the vector characterized in that the expression unit contains an IRES sequence of Beach et al. in the method of Eshar et al., since Beach et al. state, "The inclusion of an IRES sequence in the gene tapping cassette allows the fusion between cellular and viral sequence to occur at any point within the mature RNA, effectively increasing the number of possible integration sites that result in a functionally "tagged" transcript (Column 15, lines 28-33)." By employing scientific reasoning, one ordinary artisan would have combined the IRES sequence in the vector of Eshar et al. to improve the fusion between cellular and viral sequence and to tag the TCR transcripts more efficiently. An ordinary practitioner would have been motivated to substitute and combine the vector characterized in that the expression unit contains an IRES sequence of Beach et al. in the method of Eshar et al. in order to achieve the express advantages, as noted by Beach et al., of an IRES sequence in the gene tapping cassette that allows the fusion between cellular and viral sequence to occur at any point within the mature RNA, effectively increasing the number of possible integration sites that result in a functionally "tagged" transcript.

11. Claims 1-3, 8, 11, 13 and 16-26 are rejected under 35 U.S. C 103 (a) over Eshar et al. (U.S. Patent 5,906,936) (May 25, 1999) in view of in view of Stratagene Catalog (1988, Page 39).

Eshar et al teach 1-3, 8, 11, 13 and 16-23 as described above including primers for amplifying V regions of the TCRalpha and TCRbeta chains (Figure 7).

Eshar et al do not teach the motivation to combine all the TCR expression vector, primers for amplifying V regions of the TCRalpha and TCRbeta chains and host cells in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine all the TCR expression vector and host cells of Eshar et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control". (page 39, column 1).

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703)

306-5818. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun kr. Chakrabarti

Arun Chakrabarti
Patent Examiner
Art Unit 1655

December 3, 2001